Hypertension and fracture risk: impact of antihypertensive medications on bone health

Hipertensión arterial y riesgo de fractura: impacto de los medicamentos antihipertensivos en la salud ósea

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Abstract

Hypertension and osteoporosis are recognized as highly prevalent chronic conditions within the adult population, both of which have been associated with important public health concerns due to their impact on morbidity rates and healthcare expenditures. An intricate relationship between these disorders has been suggested by emerging evidence, indicating that adverse effects on bone health may be exerted by hypertension through multiple pathophysiological pathways. Furthermore, the modulation of bone metabolism by certain antihypertensive medications has been reported, leading to potential alterations in bone mineral density and modifications in the risk profile for osteoporotic fractures. The objective of this review was to analyze the available evidence on the relationship between hypertension and osteoporosis, focusing on the shared pathophysiological mechanisms and the impact of antihypertensive treatments on bone health. Through the synthesis of existing findings, a deeper understanding of the extent to which bone mineral density and fracture risk are affected by hypertension is sought. Additionally, evidence-based considerations regarding the selection of antihypertensive therapies in individuals at an increased risk for osteoporosis are provided, with the objective of optimizing treatment strategies and mitigating the potential adverse skeletal effects of long-term antihypertensive therapy.

Keywords: Hypertension, Osteoporosis, Antihypertensive drugs, Osteoporotic fractures.

Resumen

La hipertensión arterial y la osteoporosis son enfermedades crónicas de alta prevalencia en la población adulta, con importante impacto en la salud pública debido a su asociación con un aumento en la morbilidad y los elevados costos de atención médica. La evidencia emergente sugiere una relación compleja entre ambas condiciones, indicando que la hipertensión podría afectar negativamente la salud ósea a través de diversos mecanismos fisiopatológicos. Además, algunos medicamentos antihipertensivos han demostrado influir en el metabolismo óseo, lo que podría generar cambios en la densidad mineral ósea y modificar el riesgo de fracturas osteoporóticas. El objetivo de esta revisión fue analizar la evidencia disponible sobre la relación entre la hipertensión y la osteoporosis, centrándose en los mecanismos fisiopatológicos compartidos y el impacto de los tratamientos antihipertensivos en la salud ósea. A través de la síntesis de los hallazgos existentes, se busca una comprensión más profunda del grado en que la densidad mineral ósea y el riesgo de fractura se ven afectados por la hipertensión. Además, se brindan consideraciones basadas en evidencias sobre la selección de terapias antihipertensivas en individuos con mayor riesgo de osteoporosis, con el objetivo de optimizar las estrategias de tratamiento y mitigar los posibles efectos adversos sobre el esqueleto de la terapia antihipertensiva a largo plazo.

Palabras clave: Hipertensión arterial, Osteoporosis, Fármacos antihipertensivos, Fracturas osteoporóticas.

Introduction

Hypertension is recognized as one of the most prevalent chronic diseases worldwide and has been identified as a major risk factor for cardiovascular morbidity and mortality. According to the World Health Organization, it has been estimated that approximately 1.28 billion adults globally are affected by hypertension, with its prevalence continuing to increase as a consequence of population aging and the widespread adoption of unhealthy lifestyles, including physical inactivity and high-sodium dietary patterns[1]. While the contribution of hypertension to the pathogenesis of cardiovascular diseases, such as myocardial infarction and stroke, has been well established, its association with damage in other target organs, including the kidneys and the skeletal system, has also been documented[2].

Osteoporosis is a skeletal disorder characterized by a reduction in bone mineral density (BMD) and alterations in bone microarchitecture, both of which contribute to an increased susceptibility to fractures. It has been estimated that approximately 200 million individuals worldwide are affected by osteoporosis, with a particularly high prevalence observed in postmenopausal women and older adults[3]. Moreover, this condition represents a significant public health concern, as fractures related to osteoporosis impose a substantial economic burden on healthcare systems and result in a considerable decline in patients' quality of life. The primary risk factors associated with osteoporosis include advanced age, estrogen deficiency in postmenopausal women, inadequate intake of calcium and vitamin D, tobacco use, and physical inactivity[4].

Fragility fractures, which are a direct consequence of osteoporosis, have been identified as one of the leading causes of morbidity in older adults. Among these, hip, vertebral, and distal forearm fractures are the most frequently reported and have been associated with a significant increase in both disability and mortality. Furthermore, epidemiological estimates indicate that mortality rates within the first year following a hip fracture range between 20% and 30%, while approximately 50% of surviving patients experience permanent functional impairment and a subsequent loss of independence[5]. In this context, additional factors such as sarcopenia, compromised postural balance, and the presence of comorbidities—including hypertension—have been recognized as contributors to an elevated risk of falls and, consequently, an increased likelihood of fractures in this particularly vulnerable population[6].

The relationship between hypertension, osteoporosis, and fracture risk, along with the potential impact of antihypertensive medications on bone health, has received increasing attention within biomedical research. In line with these, several studies have suggested that both conditions may share common pathophysiological mechanisms, thereby prompting further investigation into their complex interactions and underlying biological pathways[7–9]. A more profound understanding of the association between hypertension and osteoporosis is warranted, specifically, exploring the mechanisms linking hypertension to osteoporosis and evaluating the effects of antihypertensive therapies on bone health could provide insights into potential preventive and therapeutic strategies. This review aims to summarize the epidemiological evidence on the association between hypertension, osteoporosis, and fracture risk, while also examining the impact of antihypertensive treatments on bone health.

HYPERTENSION AND FRACTURE RISK

The association between hypertension and the risk of osteoporotic fractures has been extensively examined in recent years, with growing evidence indicating that hypertension not only contributes to bone fragility but may also represent an independent risk factor for fragility fractures. While the underlying mechanisms of this association are not yet fully understood, several pathophysiological processes have been proposed and will be discussed in subsequent sections.

Under this context, Wada et al. (2012) conducted a cross-sectional study in postmenopausal Japanese women with hypertension, diabetes mellitus, or hyperlipidemia, finding a significant association between hypertension and vertebral fractures. In a multivariate analysis, hypertension (OR = 1.76; 95% CI: 1.11–2.80; p = 0.017), along with mammary artery calcification and advanced age, emerged as an independent risk factor[10]. These findings indicate that hypertension, arterial calcification, and osteoporosis may share common pathophysiological mechanisms, reinforcing the connection between cardiovascular and skeletal diseases in postmenopausal women. Similarly, in a prospective cohort of 1,701 women and 1,032 men over the age of 50, Yang et al. (2014) reported that hypertension was associated with lower femoral neck BMD in women (0.79 vs. 0.82 g/cm²; p = 0.02) and an increased risk of fragility fractures (HR = 1.49; 95% CI: 1.13–1.96), even after adjusting for BMD and other covariates. In contrast, among men, hypertension was associated with higher femoral neck BMD and was not linked to an increased fracture risk, suggesting potential sex-specific differences in the interaction between hypertension and bone health[11].

The association between hypertension and osteoporotic fractures has been further supported by large-scale studies, such as the meta-analysis by Li et al. (2017), which included 28 independent studies with

more than 1.4 million participants and 148,048 cases of osteoporotic fractures. It was found that hypertensive individuals had a 33% higher risk of osteoporotic fractures compared to non-hypertensive individuals (OR = 1.33; 95% CI: 1.25–1.40). This association was more pronounced in women (OR = 1.52; 95% CI: 1.30–1.79) than in men (OR = 1.35; 95% CI: 1.26–1.44), reinforcing the evidence that hypertensive women may be more vulnerable to osteoporotic fractures[12].

At the population level, Gerber et al. (2013) conducted a case-control study using data from the Rochester Epidemiology Project and found that cardiovascular diseases, particularly hypertension, were associated with an increased risk of hip fractures. Moreover, they observed a growing association over time, suggesting that cardiometabolic diseases may contribute to bone fragility[13]. Similarly, a hospitalization-based study has reported a strong association between cardiovascular diseases, including hypertension, and hip fractures. Xu et al. (2013) analyzed data from more than 860,000 hospitalized patients in China and found that the presence of cardiovascular diseases significantly increased the incidence of hip fractures (RR = 1.53; 95% CI: 1.47–1.60). This risk was particularly elevated in individuals aged 55–79 years, suggesting that hypertension and other cardiovascular conditions may have a cumulative impact on bone health with aging[14].

In this same line, Du et al. (2024) analyzed data from the China Health and Nutrition Survey and found that hypertension increased the risk of future fractures. They found that a history of fractures was not significantly associated with a higher risk of developing hypertension. This finding proposes that hypertension may act as a causal risk factor for bone fragility rather than a consequence of it[15]. Similarly, Yoo et al. (2022) examined blood pressure variability and its relationship with fractures in a cohort of over 3 million older adults in South Korea. They found that high variability in both systolic and diastolic blood pressure was associated with an increased fracture risk (HR between 1.06 and 1.07), reinforcing the idea that inadequate blood pressure regulation may compromise bone health[16]. Lastly, He et al. (2021) used a Mendelian randomization approach and found that elevated pulse pressure was associated with increased forearm BMD, but no significant association was observed between hypertension and fractures in other skeletal regions[17]. These findings suggest that hypertension may affect bone quality in a region-specific manner.

Overall, the available evidence suggests that hypertension is associated with an elevated risk of osteoporotic fractures, with this relationship being particularly pronounced in women and older adults. Moreover, although the precise mechanisms underlying this association have yet to be fully elucidated, findings from epidemiological investigations, cohort studies, and meta-analyses have consistently supported this correlation. In this same line, it has been proposed that factors such as blood pressure variability, increased pulse pressure, and excessive reductions in blood pressure levels may further contribute to an increased susceptibility to fractures. Consequently, based on the high prevalence of hypertension within the adult population, these findings carry significant implications for the prevention and clinical management of osteoporosis in hypertensive individuals, underscoring the need for an integrated approach that considers both cardiovascular and skeletal health.

ANTIHYPERTENSIVES AND FRACTURE RISK

Widely prescribed to manage cardiovascular conditions, antihypertensive medications have also drawn attention for their potential impact on bone health and fracture risk. While some evidence suggests that certain antihypertensive may help sustain BMD, other findings indicate they could inadvertently raise the likelihood of falls and fractures, especially among the elderly and individuals experiencing cognitive decline.

In this context, Dave et al. (2024) investigated the impact of initiating antihypertensive therapy on fracture risk in institutionalized older adults. Their findings indicated a significantly higher fracture incidence in patients who started antihypertensive treatment (5.4 per 100 person-years) compared to the control group (2.2 per 100 person-years). This risk was notably elevated in patients with dementia (HR: 3.28; 95% CI: 1.76–6.10) and those with high baseline blood pressure before treatment initiation (HR: 4.41 for diastolic pressure ≥80 mmHg). Additionally, antihypertensive use was associated with an increased risk of severe falls and syncope, emphasizing the need for close monitoring in high-risk populations[18].

Similarly, Weiss et al. (2017) conducted a systematic review of 21 randomized controlled trials comparing different blood pressure targets and treatment intensities. Lowering blood pressure below 150/90 mmHg was associated with reduced mortality (RR: 0.90; 95% CI: 0.83–0.98), cardiovascular events (RR: 0.77; 95% CI: 0.68–0.89), and strokes (RR: 0.74; 95% CI: 0.65–0.84). However, reducing blood pressure below 140/85 mmHg had only a marginally significant effect on cardiovascular events without a corresponding decrease in mortality. Although no increase in fall risk was observed, intensive treatment was linked to hypotension, syncope, and greater medication burden[19]. Similarly, Song et al. (2018) analyzed antihypertensive deintensification in patients with low systolic blood pressure (80–120 mmHg) and a history of falls. While reducing treatment significantly lowered recurrent fall risk in patients with systolic pressures of 80–100 mmHg, deintensification increased mortality in those with pressures of 101–120 mmHg, highlighting the need for individualized blood pressure targets in frail[20].

In contrast, the Systolic Blood Pressure Intervention Trial (SPRINT) did not report an increased risk of falls in patients undergoing intensive therapy compared to those receiving standard treatment[21].

The use of renin-angiotensin-aldosterone system (RAAS) inhibitors, such as angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs), has been widely investigated in relation to bone metabolism. Carbone et al. (2019) found that ACEI and ARB use was associated with an increased fracture risk during the first three years of treatment (HR: 3.28–6.23) but demonstrated a protective effect over the long term (>3 years) by reducing fracture risk (HR: 0.40–0.44). This pattern suggests that initial bone fragility may be linked to early alterations in calcium regulation and bone homeostasis induced by these medications[22]. Supporting this, Kao et al. (2020) conducted a retrospective cohort study in Taiwan and reported a significant reduction in fracture risk among ACEI (HR: 0.70) and ARB users (HR: 0.58), but no protective effect in patients using both drug classes simultaneously[23]. Similarly, Shea and Witham (2020) performed a retrospective analysis in Scotland, showing a 1.2% reduction in hip fracture risk and a 1.4% decrease in mortality for each year of RAAS blocker use, suggesting a long-term benefit of these drugs on bone health[24].

In line with these findings, beta-blockers have demonstrated potential protective effects on bone health. In this sense, Toulis et al. (2014) conducted a meta-analysis revealing a 15% reduction in fracture risk among beta-blocker users, with a more pronounced effect in those receiving β1-selective beta-blockers[25]. Similarly, Yavuz Keleş et al. (2020) found that β1-selective beta-blocker use was associated with higher lumbar spine BMD, though without a statistically significant reduction in fracture incidence[26]. Conversely, calcium channel blockers (CCBs) have been associated with adverse effects on bone health. Regarding this, Takaoka et al. (2013) reported that CCB use increased the risk of vertebral and non-vertebral fractures in postmenopausal women with type 2 diabetes mellitus, potentially due to an increased likelihood of falls[27]. More recently, Huang et al. (2023) confirmed that CCB use was associated with a higher fracture risk (OR: 1.07), whereas ARBs and thiazide diuretics had a protective effect[28].

Long-term use of thiazide diuretics appears to offer protective benefits against fractures. In this regard, Taipale et al. (2019) found that thiazide use for more than three years significantly reduced fracture risk in patients with Alzheimer's disease (OR: 0.68–0.77)[29]. However, Wang et al. (2019) did not find a protective effect in the general population (RR: 0.96; 95% CI: 0.83–1.09)[30]. In the same year, Charkos et al. (2019) conducted a meta-analysis concluding that case-control studies suggested a possible protective effect, while cohort studies showed no clear association[31].

Therefore, the relationship between antihypertensive medication use and fracture risk is shaped by various clinical and pharmacological factors. While some evidence suggests that ARBs, β1-selective beta-blockers, and thiazide diuretics may support BMD and lower fracture risk, CCBs and potassium-sparing diuretics have been associated with a greater likelihood of fractures. Additionally, initiating antihypertensive treatment in frail individuals may increase the risk of falls, highlighting the need for a thorough clinical evaluation to balance cardiovascular benefits with bone health, particularly in vulnerable populations.

HYPERTENSION AND OSTEOPOROSIS: SHARED PATHOPHYSIOLOGICAL MECHANISMS

Hypertension and osteoporosis are common chronic conditions in older adults, and growing evidence suggests that they may share underlying pathophysiological mechanisms (Figure 1). Osteoporosis develops when bone remodeling becomes imbalanced, with bone resorption exceeding bone formation, leading to a gradual loss of BMD and a higher risk of fractures[32]. Meanwhile, hypertension has been linked to endothelial dysfunction, increased arterial stiffness, and activation of the RAAS, processes that can contribute to microvascular damage in bone tissue and disrupt calcium homeostasis and bone metabolism[33,34].

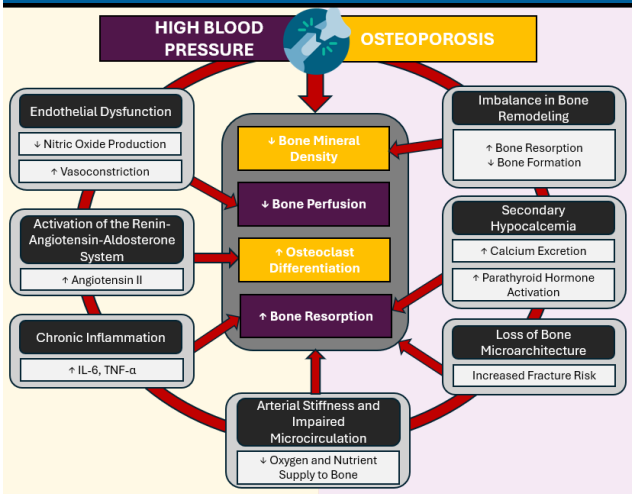
One of the primary mechanisms linking hypertension to osteoporosis is RAAS activation. Angiotensin II, through AT1 receptor stimulation, promotes osteoclast differentiation and bone resorption, accelerating bone loss[35]. Additionally, inhibition of RAAS with ARBs or ACEIs has been shown to reduce osteoclastic activity and slow bone resorption, though the clinical impact on BMD and fracture risk remains a topic of debate[36,37]. Another mechanism is the increased urinary calcium excretion, which leads to secondary hypocalcemia and subsequent activation of parathyroid hormone. This activation stimulates bone resorption to maintain calcium homeostasis, ultimately resulting in greater bone loss and an increased risk of fractures[38]. In animal models, hypertension has been linked to elevated bone porosity and reduced bone mineral density, indicating an increase in bone resorption[39].

In individuals with hypertension, dysfunction in the endothelium often leads to lower nitric oxide (NO) production, which can disrupt blood flow to the bones and reduce the activity of osteoblasts. Therefore, when NO levels are reduced, osteoclasts tend to become more active, accelerating bone loss over time[40]. Moreover, some studies suggests that NO donors could help preserve BMD, opening the door to potential therapeutic strategies for reducing osteoporosis risk in people with hypertension[41].

In addition, low-grade chronic inflammation has also emerged as a key factor linking hypertension and osteoporosis at the molecular level. Studies indicate that

individuals with high blood pressure often have elevated levels of inflammatory molecules like interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), both of which contribute to bone resorption while slowing the formation of new bone[42]. Furthermore, endothelial dysfunction has also been implicated in the disruption of bone microcirculation, which compromises the delivery of oxygen and important nutrients required for bone maintenance, ultimately contributing to skeletal fragility and an increased risk of fractures[43].

Figure 1. Pathophysiological Mechanisms Between Hypertension and Osteoporosis.



The effects of antihypertensive medications on bone metabolism vary depending on their mechanism of action, influencing BMD and fracture risk. Bone health has been shown to be supported by thiazide diuretics through a reduction in urinary calcium excretion, which contributes to the preservation of bone mass and a lower incidence of fractures[41]. Also, beta-blockers have been suggested to reduce bone resorption and improve BMD by modulating sympathetic activity, although their overall effect on fracture risk remains uncertain[42,43]. In contrast, an increase in calcium excretion has been observed with loop diuretics such as furosemide, potentially leading to bone loss and a higher risk of fractures. Moreover, CCBs have been associated with a higher risk of fractures, possibly due to their influence on muscle function and an increased propensity for falls[44,45].

The interplay between hypertension, antihypertensive medications, and osteoporosis is influenced by multiple physiological factors, including RAAS activation, endothelial dysfunction, and chronic inflammation. While some antihypertensives may support bone health, others can raise the risk of fractures. For those already vulnerable to osteoporosis, choosing the right treatment requires a careful balance, ensuring effective blood pressure control while also safeguarding bone strength.

Conclusions

This review highlights the complex connection between hypertension and osteoporosis, two conditions that often go as comorbidities, especially in older adults. While hypertension is widely recognized for its impact on cardiovascular health, growing evidence suggests it may also play a role in bone weakening, increasing the risk of fractures. Several biological mechanisms may help explain this link, including the involvement of the RAAS system, low-grade chronic inflammation, endothelial dysfunction, and disruptions in calcium balance. Also, variations in blood pressure and arterial stiffness may reduce blood flow to bones, potentially affecting their ability to repair and maintain strength over time.

The effects of antihypertensive medications on bone health vary depending on the type of drug. Some, such as thiazide diuretics and β1-selective beta-blockers, appear to help preserve bone mineral density and lower fracture risk. In contrast, calcium channel blockers and loop diuretics have been linked to a higher risk of fractures, possibly due to their influence on calcium balance and an increased risk of falls. RAAS blockers, including ACE inhibitors and ARBs, have shown mixed results—while they may help slow bone loss over time, their role in fracture prevention is still uncertain.

Considering the high prevalence of both conditions among older adults, treatment approaches should address them simultaneously, taking into account that is equally important to select medications that do not compromise bone health. Some antihypertensive drugs may have unintended effects on bone density or fracture risk, but more research is needed to clarify these connections and guide safer treatment choices.

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